

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

WHAT IS CLAIMED IS:

1. A method of treating acne in a human in need thereof comprising administering systemically to said human a tetracycline compound in an amount that is effective to treat acne but has substantially no antibiotic activity, without administering a bisphosphonate compound.
2. A method according to Claim 1, wherein said acne is acne vulgaris, cystic acne, acne atrophica, bromide acne, chlorine acne, acne conglobata, acne cosmetica, acne detergentans, epidemic acne, acne estivalis, acne fulminans, halogen acne, acne indurata, iodide acne, acne keloid, acne mechanica, acne papulosa, pomade acne, premenstrual acne, acne pustulosa, acne rosacea, acne scorbutica, acne scrofulosorum, acne urticata, acne varioliformis, acne venenata, propionic acne, acne excoriee, gram negative acne, steroid acne, or nodulocystic acne.
3. A method according to Claim 1, wherein said tetracycline compound is an antibiotic tetracycline compound administered in an amount which is 10-80% of the antibiotic amount.
4. A method according to Claim 1, wherein said tetracycline compound is doxycycline administered twice a day in a dose of 20 mg.
5. A method according to Claim 1, wherein said tetracycline compound is minocycline administered once a day in a dose of 38 mg.
6. A method according to Claim 1, wherein said tetracycline compound is minocycline administered twice a day in a dose of 38 mg.
7. A method according to Claim 1, wherein said tetracycline compound is minocycline administered three times a day in a dose of 38 mg.

8. A method according to Claim 1, wherein said tetracycline compound is minocycline administered four times a day in a dose of 38 mg.
9. A method according to Claim 1, wherein said tetracycline compound is tetracycline administered once a day in a dose of 60 mg/day.
10. A method according to Claim 1, wherein said tetracycline compound is tetracycline administered twice a day in a dose of 60 mg/day.
11. A method according to Claim 1, wherein said tetracycline compound is tetracycline administered three times a day in a dose of 60 mg/day.
12. A method according to Claim 1, wherein said tetracycline compound is tetracycline administered four times a day in a dose of 60 mg/day.
13. A method according to Claim 1, wherein said tetracycline compound is an antibiotic tetracycline compound administered in an amount which results in a serum concentration which is 10-80% of the minimum antibiotic serum concentration.
14. A method according to Claim 1, wherein said tetracycline compound is doxycycline administered in an amount which results in a serum concentration which is 1.0 $\mu\text{g/ml}$.
15. A method according to Claim 1, wherein said tetracycline compound is minocycline administered in an amount which results in a serum concentration which is 0.8 $\mu\text{g/ml}$.
16. A method according to Claim 1, wherein said tetracycline compound is tetracycline administered in an amount which results in a serum concentration which is 0.5 $\mu\text{g/ml}$.

17. A method according to Claim 3 or 13, wherein said antibiotic tetracycline compound is doxycycline, minocycline, tetracycline, oxytetracycline, chlortetracycline, demeclocycline or pharmaceutically acceptable salts thereof.

18. A method according to Claim 17, wherein said antibiotic tetracycline compound is doxycycline.

19. A method according to Claim 18, wherein said doxycycline is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 $\mu\text{g/ml}$.

20. A method according to Claim 18, wherein said doxycycline is administered in an amount of 20 milligrams twice daily.

21. A method according to Claim 19, wherein said doxycycline is administered by sustained release over a 24 hour period.

22. A method according to Claim 21, where said doxycycline is administered in an amount of 40 milligrams.

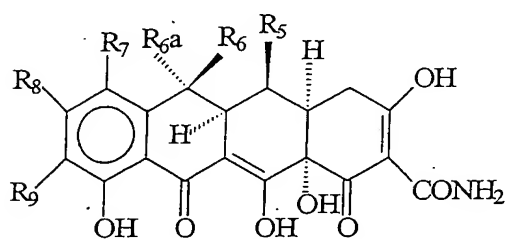
23. A method according to Claim 1, wherein said tetracycline compound is a non-antibiotic tetracycline compound.

24. A method according to Claim 23, wherein said non-antibiotic tetracycline compound is:

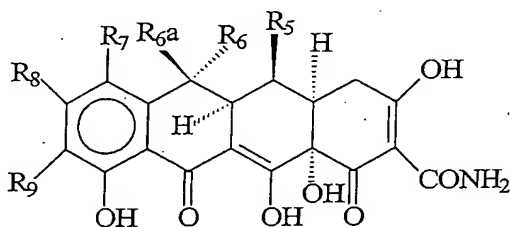
- 4-de(dimethylamino)tetracycline (CMT-1),
- tetracyclinonitrile (CMT-2),
- 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline (CMT-3),
- 4-de(dimethylamino)-7-chlorotetracycline (CMT-4),
- tetracycline pyrazole (CMT-5)

4-hydroxy-4-de(dimethylamino)tetracycline (CMT-6),
 4-de(dimethylamino)-12 α -deoxytetracycline (CMT-7),
 6- α -deoxy-5-hydroxy-4-de(dimethylamino)tetracycline (CMT-8),
 4-de(dimethylamino)-12 α -deoxyanhydrotetracycline (CMT-9), or
 4-de(dimethylamino)minocycline (CMT-10).

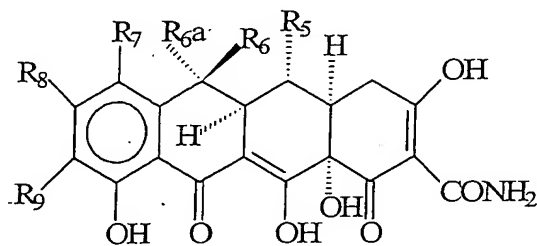
25. A method according to Claim 23, wherein the non-antibiotic tetracycline compound is selected from the group consisting of:



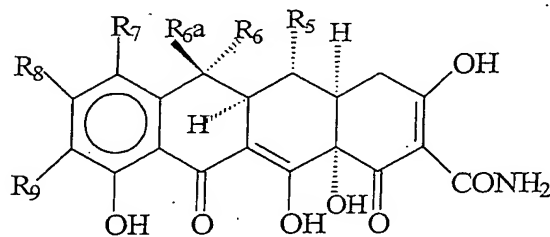
Structure C



Structure D



Structure E



Structure F

wherein:

R7 is selected from the group consisting of hydrogen, amino, nitro, mono(lower alkyl) amino, halogen, di(lower alkyl)amino, ethoxythiocarbonylthio, azido, acylamino, diazonium, cyano, and hydroxyl;

R6-a is selected from the group consisting of hydrogen and methyl;

R6 and R5 are selected from the group consisting of hydrogen and hydroxyl;

R8 is selected from the group consisting of hydrogen and halogen;

R9 is selected from the group consisting of hydrogen, amino, azido, nitro, acylamino, hydroxy, ethoxythiocarbonylthio, mono(lower alkyl) amino, halogen, diazonium, di(lower alkyl)amino and $\text{RCH}(\text{NH}_2)\text{CO}$;

R is hydrogen or lower alkyl; and

pharmaceutically acceptable salts thereof; with the following provisos:

when either R7 and R9 are hydrogen then R8 must be halogen; and

when R6-a, R6, R5 and R9 are all hydrogen and R7 is hydrogen, amino, nitro, halogen, dimethylamino or diethylamino, then R8 must be halogen; and

when R6-a is methyl, R6 and R9 are both hydrogen, R5 is hydroxyl, and R7 is hydrogen, amino, nitro, halogen or diethylamino, then R8 is halogen; and

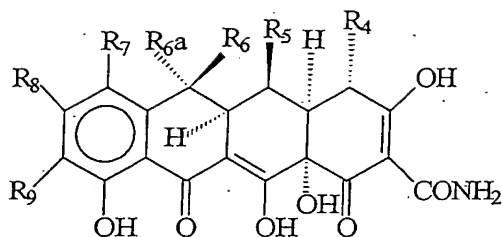
when R6-a is methyl, R6 is hydroxyl, R5, R7 and R9 are all hydrogen, then R8 must be halogen; and

when R6-a, R6 and R5 are all hydrogen, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and

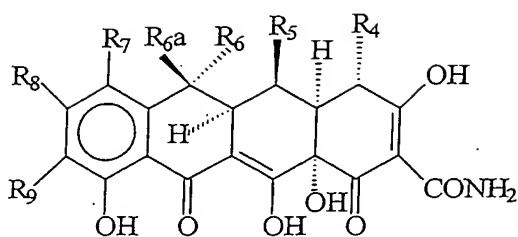
when R6-a is methyl, R6 is hydrogen, R5 is hydroxyl, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and

when R6-a is methyl, R6, R5 and R9 are all hydrogen and R7 is cyano, then R8 must be halogen.

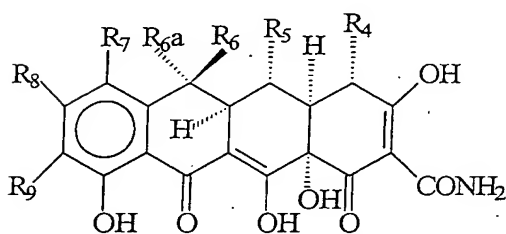
26. A method according to Claim 23, wherein the non-antibiotic tetracycline compound is selected from the group consisting of:



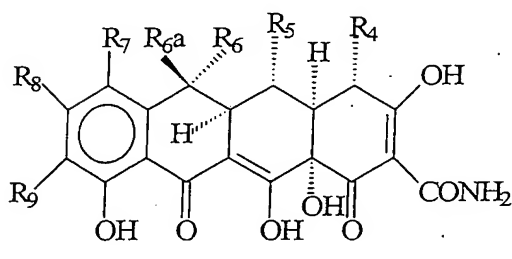
Structure G



Structure H



Structure I



Structure J

wherein:

R7 is selected from the group consisting of hydrogen, amino, nitro, mono(lower alkyl) amino, halogen, and di(lower alkyl)amino, ethoxythiocarbonylthio, azido, acylamino, diazonium, cyano, and hydroxyl;

R6-a is selected from the group consisting of hydrogen and methyl;

R6 and R5 are selected from the group consisting of hydrogen and hydroxyl;

R4 is selected from the group consisting of NOH, N-NH-A, and NH-A, where A is a lower alkyl group;

R8 is selected from the group consisting of hydrogen and halogen;

R9 is selected from the group consisting of hydrogen, amino, azido, nitro, acylamino, hydroxy, ethoxythiocarbonylthio, mono(lower alkyl) amino, halogen, di(lower alkyl)amino and $RCH(NH_2)CO$;

R is hydrogen or lower alkyl; and

pharmaceutically acceptable salts thereof; with the following provisos:

when R4 is NOH, N-NH-alkyl or NH-alkyl and R7, R6-a, R6, R5, and R9 are all hydrogen, then R8 must be halogen; and

when R4 is NOH, R6-a is methyl, R6 is hydrogen or hydroxyl, R7 is halogen, R5 and R9 are both hydrogen, then R8 must be halogen; and

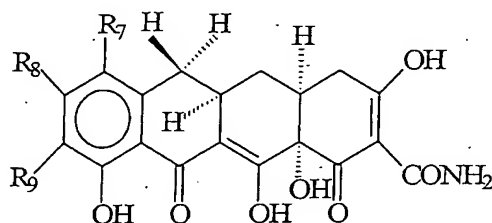
when R4 is N-NH-alkyl, R6-a is methyl, R6 is hydroxyl and R7, R5, R9 are all hydrogen, then R8 must be halogen; and

when R4 is NH-alkyl, R6-a, R6, R5 and R9 are all hydrogen, R7 is hydrogen, amino, mono(lower alkyl)amino, halogen, di(lower alkyl)amino or hydroxyl, then R8 must be halogen; and

when R4 is NH-alkyl, R6-a is methyl, R6 and R9 are both hydrogen, R5 is hydroxyl; and R7 is mono(lower alkyl)amino or di(lower alkyl)amino, then R8 must be halogen; and

when R4 is NH-alkyl, R6-a is methyl, R6 is hydroxy or hydrogen and R7, R5, and R9 are all be hydrogen, then R8 must be halogen.

27. A method according to Claim 23 wherein the non-antibiotic tetracycline compound is selected from the group consisting of:



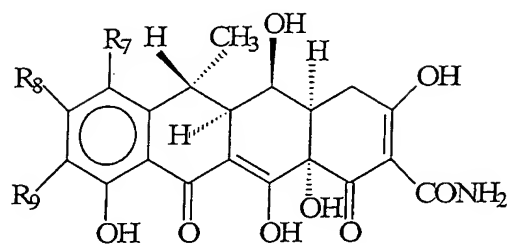
Structure K

wherein: R7, R8, and R9 taken together in each case, have the following meanings:

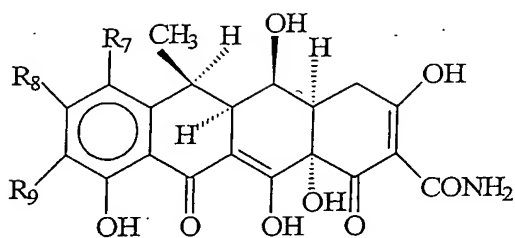
R7	R8	R9
azido	hydrogen	hydrogen
dimethylamino	hydrogen	azido
hydrogen	hydrogen	amino
hydrogen	hydrogen	azido
hydrogen	hydrogen	nitro

dimethylamino	hydrogen	amino
acylamino	hydrogen	hydrogen
hydrogen	hydrogen	acylamino
amino	hydrogen	nitro
hydrogen	hydrogen	(N,N-dimethyl)glycylamino
amino	hydrogen	amino
hydrogen	hydrogen	ethoxythiocarbonylthio
dimethylamino	hydrogen	acylamino
dimethylamino	hydrogen	diazonium
dimethylamino	chloro	amino
hydrogen	chloro	amino
amino	chloro	amino
acylamino	chloro	acylamino
amino	chloro	hydrogen
acylamino	chloro	hydrogen
monoalkylamino	chloro	amino
nitro	chloro	amino
dimethylamino	chloro	acylamino
dimethylamino	chloro	dimethylamino
hydrogen	hydrogen	dimethylamino
dimethylamino	hydrogen	hydrogen

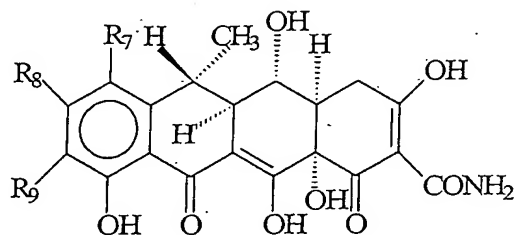
and



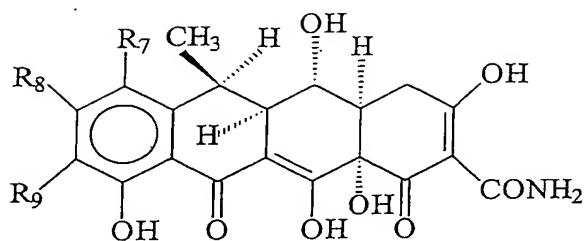
Structure L



Structure M



Structure N

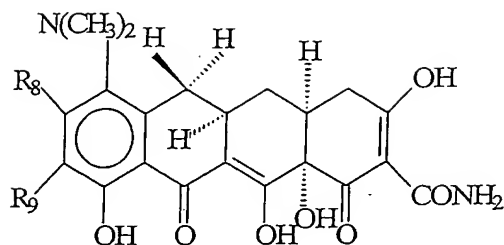


Structure O

wherein: R7, R8, and R9 taken together in each case, have the following meanings:

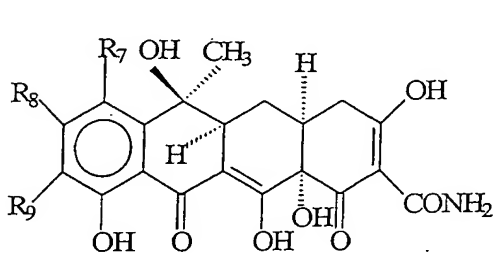
R7	R8	R9
azido	hydrogen	hydrogen
dimethylamino	hydrogen	azido
hydrogen	hydrogen	amino
hydrogen	hydrogen	azido
hydrogen	hydrogen	nitro
dimethylamino	hydrogen	amino
acylamino	hydrogen	hydrogen
hydrogen	hydrogen	acylamino
amino	hydrogen	nitro
hydrogen	hydrogen	(N,N-dimethyl)glycylamino
amino	hydrogen	amino
hydrogen	hydrogen	ethoxythiocarbonylthio
dimethylamino	hydrogen	acylamino
hydrogen	hydrogen	diazonium
hydrogen	hydrogen	dimethylamino
diazonium	hydrogen	hydrogen
ethoxythiocarbonylthio	hydrogen	hydrogen
dimethylamino	chloro	amino
amino	chloro	amino
acylamino	chloro	acylamino
hydrogen	chloro	amino
amino	chloro	hydrogen
acylamino	chloro	hydrogen
monoalkylamino	chloro	amino
nitro	chloro	amino

and

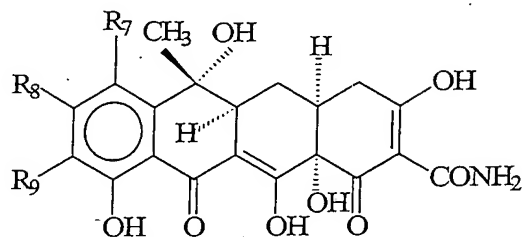


Structure P

wherein: R8 is hydrogen or halogen and R9 is selected from the group consisting of nitro, (N,N-dimethyl)glycylamino, and ethoxythiocarbonylthio; and



Structure Q



Structure R

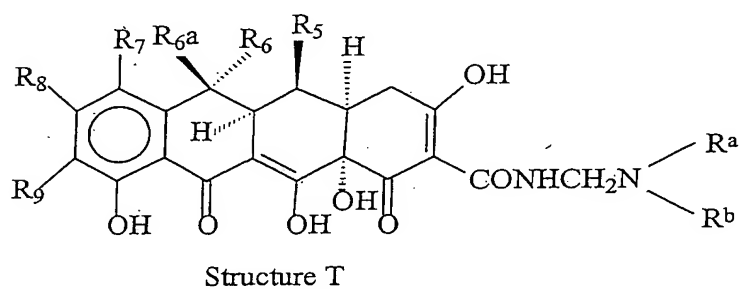
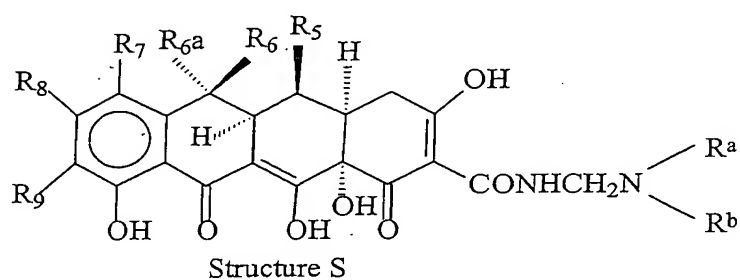
wherein: R7, R8, and R9 taken together in each case, have the following meanings:

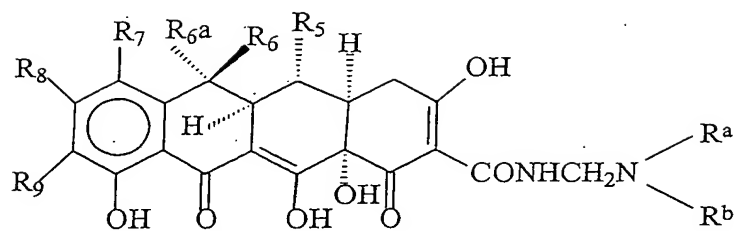
R7	R8	R9
amino	hydrogen	hydrogen
nitro	hydrogen	hydrogen
azido	hydrogen	hydrogen
dimethylamino	hydrogen	azido
hydrogen	hydrogen	amino
hydrogen	hydrogen	azido
hydrogen	hydrogen	nitro
bromo	hydrogen	hydrogen
dimethylamino	hydrogen	amino
acylamino	hydrogen	hydrogen
hydrogen	hydrogen	acylamino
amino	hydrogen	nitro
hydrogen	hydrogen	(N,N-dimethyl)glycylamino
amino	hydrogen	amino
diethylamino	hydrogen	hydrogen
hydrogen	hydrogen	ethoxythiocarbonylthio

dimethylamino	hydrogen	methylamino
dimethylamino	hydrogen	acylamino
dimethylamino	chloro	amino
amino	chloro	amino
acylamino	chloro	acylamino
hydrogen	chloro	amino
amino	chloro	hydrogen
acylamino	chloro	hydrogen
monoalkylamino	chloro	amino
nitro	chloro	amino

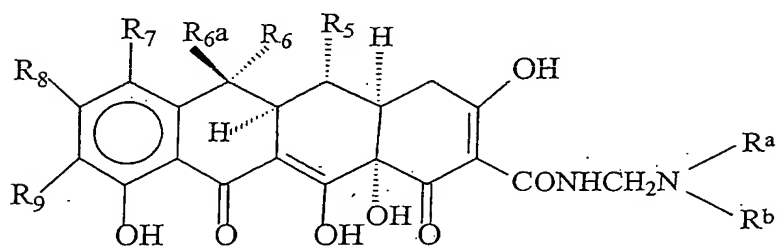
and pharmaceutically acceptable salts thereof.

28. A method according to Claim 23, wherein the non-antibiotic tetracycline compound is selected from the group consisting of:

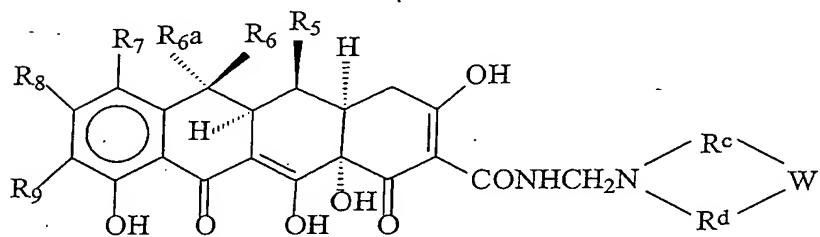




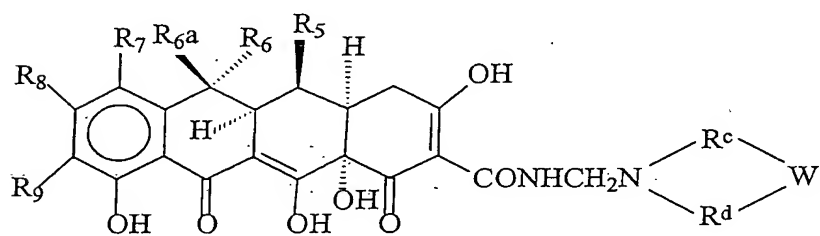
Structure U



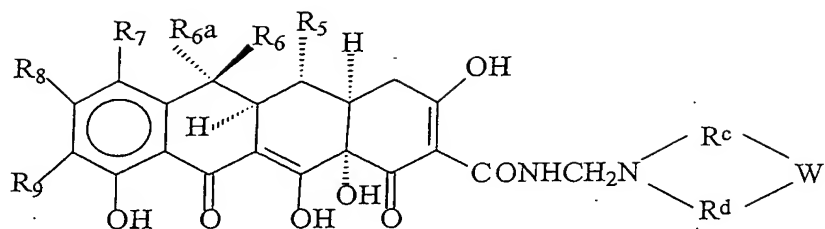
Structure V



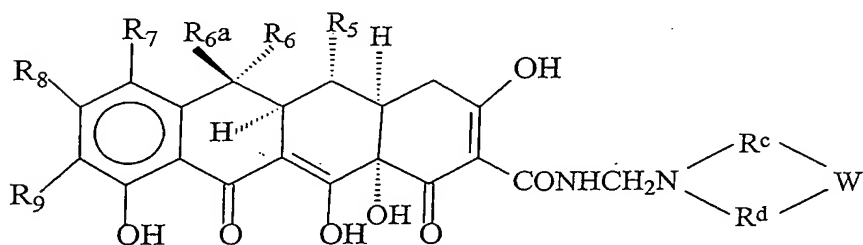
Structure W



Structure X



Structure Y



Structure Z

wherein:

R7 is selected from the group consisting of hydrogen, amino, nitro, mono(lower alkyl) amino, halogen, di(lower alkyl)amino, ethoxythiocarbonylthio, azido, acylamino, diazonium, cyano, and hydroxyl;

R6-a is selected from the group consisting of hydrogen and methyl;

R6 and R5 are selected from the group consisting of hydrogen and hydroxyl;

R8 is selected from the group consisting of hydrogen and halogen;

R9 is selected from the group consisting of hydrogen, amino, azido, nitro, acylamino, hydroxy, ethoxythiocarbonylthio, mono(lower alkyl) amino, halogen, diazonium, di(lower alkyl)amino and $RCH(NH_2)CO$;

R is hydrogen or lower alkyl;

R^a and R^b are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl and 1-methylethyl with the proviso that R^a and R^b cannot both be hydrogen;

R^c and R^d are, independently, $(CH_2)_nCHR^e$ wherein n is 0 or 1 and R^e is selected from the group consisting of hydrogen, alkyl, hydroxy, lower(C_1 - C_3) alkoxy, amino, or nitro; and,

W is selected from the group consisting of $(\text{CHR}^e)_m$ wherein m is 0-3 and said R^e is as above, NH, $\text{N}(\text{C}_1\text{-C}_3)$ straight chained or branched alkyl, O, S and $\text{N}(\text{C}_1\text{-C}_4)$ straight chain or branched alkoxy; and,
pharmaceutically acceptable salts thereof.

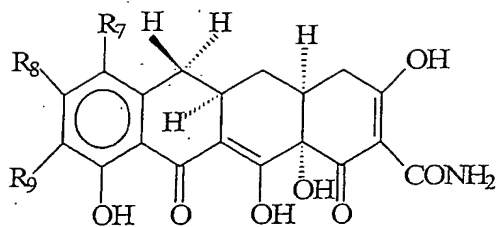
29. A method according to Claim 16, wherein the non-antibiotic tetracycline compound selected from the group consisting of structures S-Z has the following provisos:

- when either R7 and R9 are hydrogen then R8 must be halogen; and
- when R6-a, R6, R5 and R9 are all hydrogen and R7 is hydrogen, amino, nitro, halogen, dimethylamino or diethylamino, then R8 must be halogen; and
- when R6-a is methyl, R6 and R9 are both hydrogen, R5 is hydroxyl, and R7 is hydrogen, amino, nitro, halogen or diethylamino, then R8 is halogen; and
- when R6-a is methyl, R6 is hydroxyl, R5, R7 and R9 are all hydrogen, then R8 must be halogen; and
- when R6-a, R6 and R5 are all hydrogen, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and
- when R6-a is methyl, R6 is hydrogen, R5 is hydroxyl, R9 is methylamino and R7 is dimethylamino, then R8 must be halogen; and
- when R6-a is methyl, R6, R5 and R9 are all hydrogen and R7 is cyano, then R8 must be halogen.

30. A method according to Claim 1, wherein said tetracycline compound has a photoirritancy factor of less than the photoirritancy factor of doxycycline.

31. A method according to Claim 1, wherein said tetracycline compound has a photoirritancy factor from about one to about two.

32. A method according to Claim 31, wherein said tetracycline compound has a general formula:

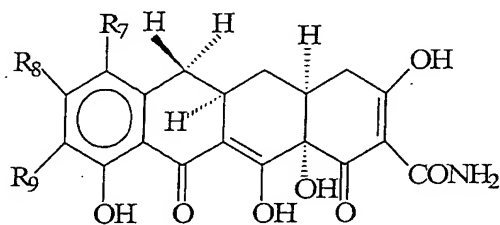


Structure K

wherein R7, R8, and R9 taken together are, respectively, hydrogen, hydrogen and dimethylamino.

33. A method according to Claim 1, wherein said tetracycline compound has a photoirritancy factor from about 1.0 to about 1.2.

34. A method according to Claim 33, wherein said tetracycline compound is selected from the group consisting of:



Structure K

wherein R7, R8, and R9 taken together in each case, have the following meanings:

R7

R8

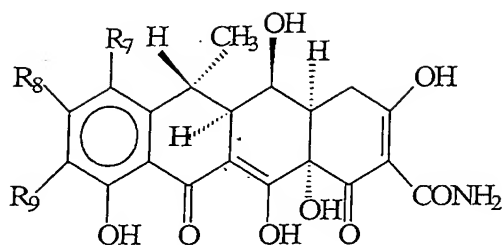
R9

hydrogen
hydrogen

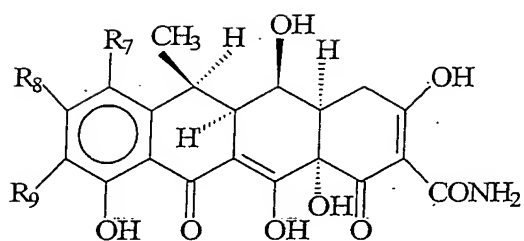
hydrogen
hydrogen

amino
palmitamide

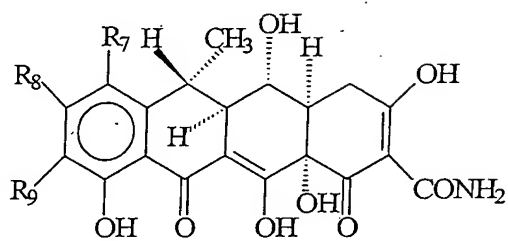
and



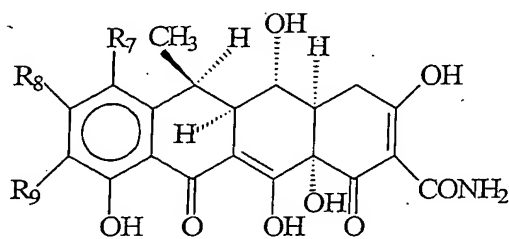
Structure L



Structure M



Structure N



Structure O

wherein R7, R8, and R9 taken together in each case, have the following meanings:

R7

hydrogen
hydrogen
hydrogen
hydrogen

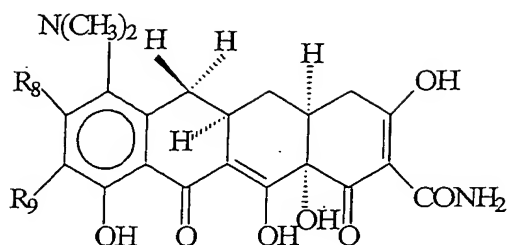
R8

hydrogen
hydrogen
hydrogen
hydrogen

R9

acetamido
dimethylaminoacetamido
nitro
amino

and



Structure P

wherein R8, and R9 taken together are, respectively, hydrogen and nitro.

35. A method according to Claim 1, wherein said systemic administration is oral administration, intravenous injection, intramuscular injection, subcutaneous administration, transdermal administration or intranasal administration.

36. A method of treating acne in a human in need thereof comprising administering to said human an effective amount of a non-antibiotic tetracycline compound without administering a bisphosphonate compound.

37. A method according to Claim 36, wherein said administration is topical administration.

38. A method according to Claim 36, wherein said administration is systemic administration.

39. A method for reducing the number of comedones in a human in need thereof comprising administering systemically to said human a tetracycline compound in an amount that is effective to reduce the number of comedones but has substantially no antibiotic activity.

40. A method according to Claim 39, wherein said tetracycline compound is doxycycline.

41. A method according to Claim 40, wherein said doxycycline is administered in a daily amount of from about 30 to about 60 milligrams but maintains a concentration in human plasma below the threshold for a significant antibiotic effect.

42. A method according to Claim 40, wherein said doxycycline is administered in an amount of approximately 20 milligrams twice daily.

43. A method according to Claim 39, wherein said tetracycline compound is administered without administering a bisphosphonate.

44. A method for inhibiting oxidation of melanin in a human in need thereof comprising administering systemically to said human a tetracycline compound in an amount that is effective to inhibit oxidation of melanin but has substantially no antibiotic activity.

45. A method for inhibiting lipid-associated abnormal follicular differentiation in a human in need thereof comprising administering systemically to said human a tetracycline compound in an amount that is effective to inhibit lipid-associated abnormal follicular differentiation but has substantially no antibiotic activity.